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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/826,982

04/15/2004

Celia Dominguez

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2634

7590

04/13/2006

US Patent Operations/RVP
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EXAMINER

HABTE, KAHSAI

ART UNIT

PAPER NUMBER

1624

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/826,982

Applicant(s)

DOMINGUEZ ET AL.

Examiner

Kahsay Habte

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1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

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DETAILED ACTION

1. Claims 1-11 are pending in this application.

Election/Restriction

2. Applicant's election of a single disclosed species: {4-[5-methyl-6-piperidin-4-yl-3-(3-trifluoromethyl-phenyl)-pyridazine-4-yl]-pyrimidine-2-yl}-(1-phenyl-ethyl)-amine is acknowledged. The examiner searched the elected species and find no prior art. The search was expanded until a prior art was found.

Information Disclosure Statement

3. Applicant's Information Disclosure Statement, filed on 4/15/2004 and 11/01/2004 has been acknowledged. Please refer to Applicant's copies of the 1449 submitted herewith.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by El-Dean et al. Pharmazie (1998), 53(12), 839-843. Cited reference at page 840 teaches a compound of interest: 1-[5,6-diphenyl-3-(1-piperdiny)-4-pyridaziny]-Ethanone (see

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compound 17). Said compound is the same as applicants when applicant's compound formula has the following substituents:

$X^1 = X^2 = N$; $R^2 = \text{piperidinyl}$; $R^3 = R^4 = \text{phenyl}$ and $R^1 = \text{COCH}_3$

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There has been recited a method of treating inflammation or treating myriad diseases recited in claim 4, but the specification is not enabled for such a scope.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the claims is not adequately enabled solely based on the activity related to antiviral activity provided in the specification. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical therapeutic agents having antiviral activity, useful to treat viral infections in general. Test procedures and assays are provided in the specification at page 91 only for 11 compounds and it is concluded that the representative compounds of formula (I) demonstrated positive inhibitory activity with IC_{50} ranging from 0.00013 1M to 2.51119 5 1M, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The disorders encompassed by the instant claims (i.e. viral infections in general), some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Enablement for the scope of "**inflammation**" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by

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which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others.

Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is

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caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths, behind only heart disease and cancer. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Effective acute drug treatment of the stroke itself has so far proved to be beyond the reach of medical science. Major efforts have certainly been pressed in the area of neuroprotective therapeutics. Those studied have included use of Ca antagonists such as Levemopamil and flunarizine, to suppress neuronal calcium influx; NMDA antagonists (both competitive, such as APV and CPP, and non-competitive such as chlorpromazine, ifenprodil and Mg salts) as well as AMPA and kainate antagonists to block post-ischemic receptor-operated calcium channels; attempts to block arachidonic acid cascade or elimination of its metabolic products with agents such as lipogenase inhibitors and thromboxane; use of free oxygen radical scavengers such as superoxide dismutase, alpha-tocopherol, or allopurinol to inhibit the lipid peroxidation that damages cell membranes, which may indirectly help prevent intracellular calcium overload; anti-edema agents such as corticosteroids; use of 5-HT_{1A} receptor agonists to suppress 5-HT concentrations in the hippocampal extracellular space; use of CRF receptor antagonists to inhibit excitotoxic brain damage; use of serotonin 1A agonists such as ipsapirone, or adenosine modulators such as vinpocetine, to stimulate adenosine, which may act as a protective agent by hyperpolarizing the postsynaptic neuron; use of platelet aggregation inhibitors such as prostacycline and ticlopidine, and other approaches as well.

Despite this vast outpouring of research, the skill level in this art is sufficiently low relative to the difficulty of the task that obtaining a neuroprotective treatment of stroke was, as of the filing date, not yet possible. Hence, accomplishing such a goal involves more than routine experimentation. As evidence for this, there is cited Chalmers (TiPS

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Vol 17, pages 166-172 April 1996), which states flatly on page 170 that, "At present, there are no effective neuroprotective agents that can clinically ameliorate the effects of stroke in humans." For example, Pentoxifylline has been one of the most intensely studied, with dozens of studies published on its properties. It appears to have a wide variety of effects on leucocytes, erythrocytes, neutrophils, plasma fibrinogen levels. These result in a wide-ranging ability to increase blood flow, resulting in effectiveness in some vascular disorders, especially intermittent claudication. Research with different administration methods, or different subcategories of stroke may well result in the discovery of how to get this drug to work, but the slowness and difficulty of this research shows clearly that this involves undue, not routine experimentation. Applicants' compounds have been subjected to far less study.

The central characteristic of **Alzheimer's disease** is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory or it is believed that too much stimulation of nerve cells by glutamate may be responsible for the degeneration of nerves that occur in Alzheimer's disease. Like other neurotransmitters, glutamate is produced and released by nerve cells in the brain. The released glutamate then travels to nearby nerve cells where it attaches to a receptor on the surface of the cells called the N-methyl-D-aspartate (NMDA) receptor. Drugs such as memantine blocks the receptor and thereby decreases the effects of glutamate. It is thought that by blocking the NMDA receptor and the effects of glutamate, memantine may protect nerve cells from excess stimulation by glutamate. Thus, Alzheimer's

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disease can be treated by Acetylcholinesterase inhibitors that reduce the depletion of acetylcholine or by drugs that inhibit NMDA receptor. The skill level in the art is so low that the only treatments available to this day are drugs that inhibit Acetylcholinesterase or drugs that inhibit NMDA receptor that decreases the effects of glutamate. Applicants' compounds do not do this. Thus, the enablement rejection is proper.

Like wise, the specification is not enabled for the treatment of myriad diseases recited in claim 4. Note that the diseases recited in claim 4 are extremely different one from the other. It is recommended that applicants delete claims 3-4 to overcome this rejection.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 and claims dependent thereon are rejected because there is no definition for variable R. What is the definition of variable R? Note that X^1 is defined as C(R) or N, but there is no definition for variable R.

Claim Objections

7 Claims 10-11 are objected to because they duplicate claim 9. Claims 10-11 recite intended use, but said use has no patentable weight. Note that claims 9 and 10-11 are drawn to the same method (i.e. manufacture of a medicament).

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Kahsay Hapte', written in a cursive style.

Kahsay Hapte
Primary Examiner
Art Unit 1624

KH
April 10, 2006